Tick-borne diseases and viruses in cancer and unexplained syndromes

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Armin Schwarzbach MD PhD

Medical doctor and
Specialist for laboratory medicine
Augsburg, Germany

ArminLabs
Laboratory for tick-borne diseases

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DIAGNOSING TICK-BORNE DISEASES

PART I: Cancer and infections

What cancers are tick-borne diseases (TBDs) associated with?

Haematologic disorders that can develop into malignancies

- Myelodysplastic syndromes
- Leukaemia
- Monoclonal Gammopathy of Undetermined Significance (MGUS)
- Lymphomas/Non-Hodgkin's Lymphoma
- … and others

Source: http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/pulmonary/sarcoidosis/

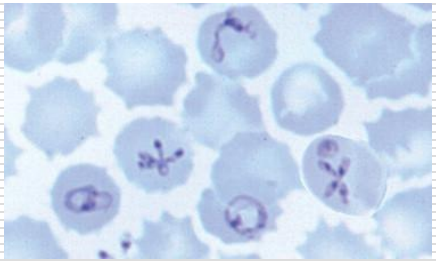
Question:

Why primarily blood-related disorders/cancers

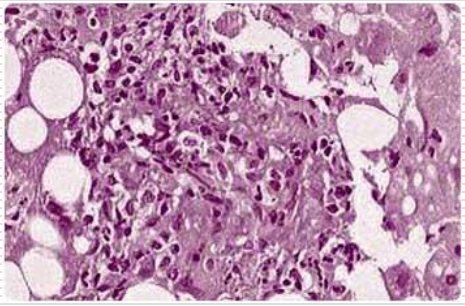
?

Lyme and co-infections find the blood/lymph a welcome host

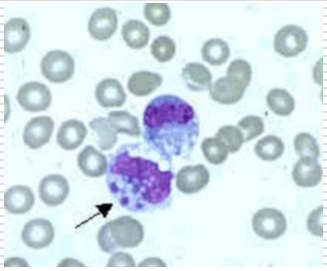
Babesia:
red blood cells

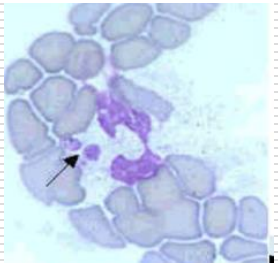


Coxiella/
Q fever



Ehrlichia:
leukocytes
and granulo-
cytes

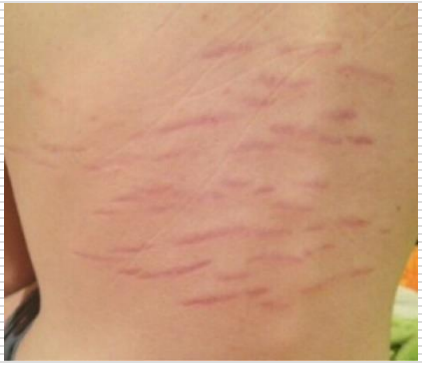


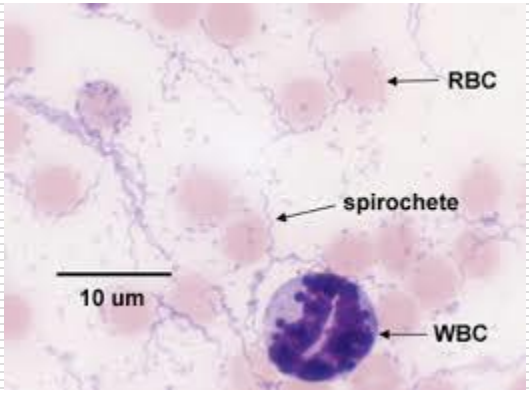


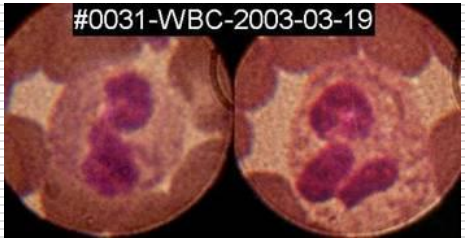
Borrelia spirochetes in the blood

.....within white blood cells:

Bartonella







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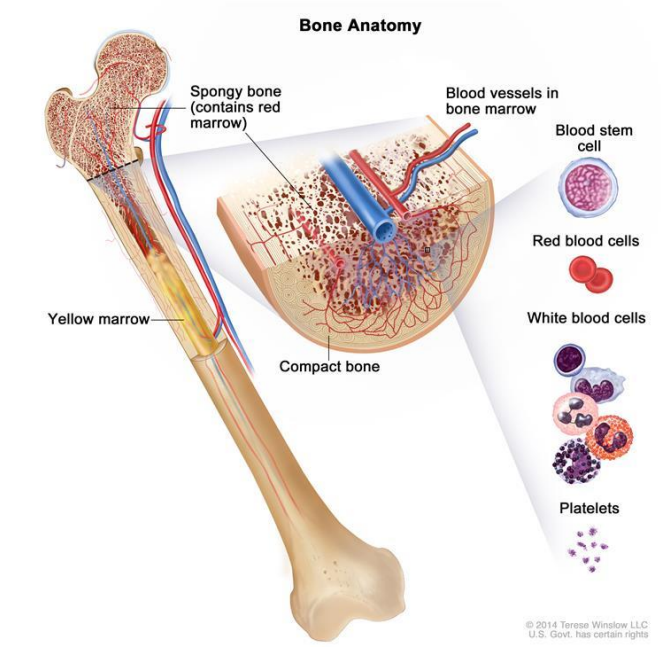
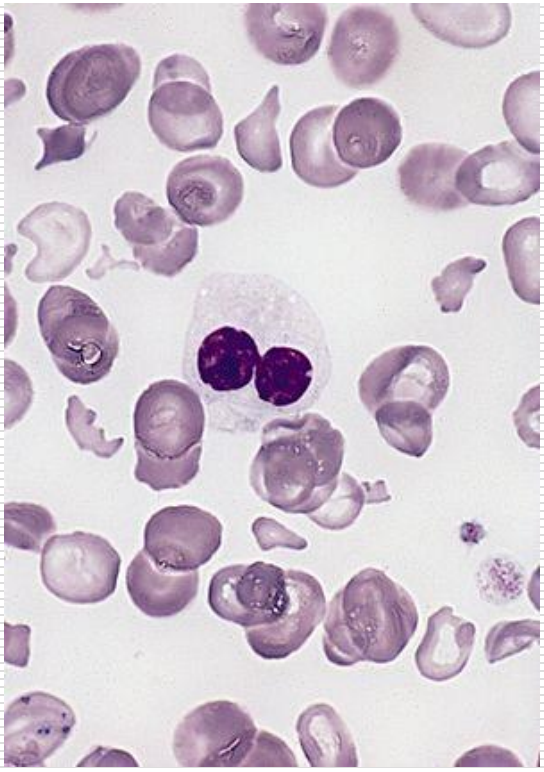
DIAGNOSING TICK-BORNE DISEASES

Myelodysplastic Syndromes (MDS)

Myelodysplastic Syndromes **(MDS) are a group of diverse bone marrow disorders in which the bone marrow does not produce enough healthy blood cells. MDS is often referred to as a "bone marrow failure disorder".**



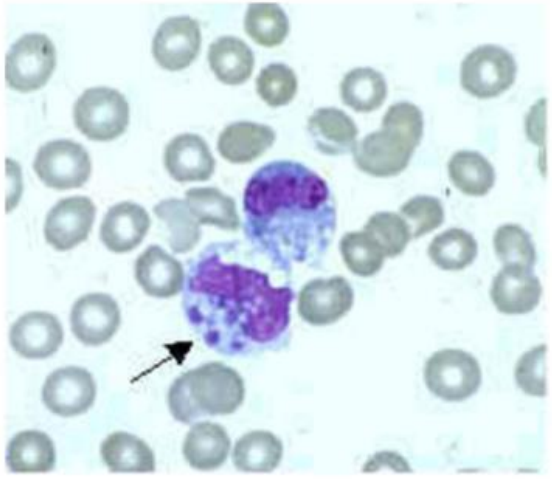


Myelodysplastic syndromes / Leukaemia

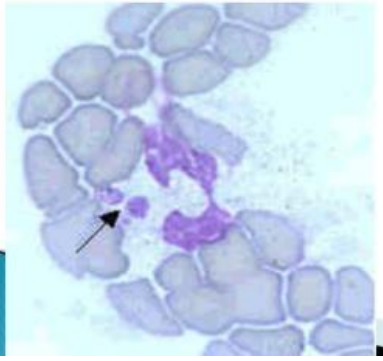
Myelodysplastic diseases and Ehrlichia: Consideration of a possible etiologic connection and mechanisms of pathogenesis, in 12th annual symposium on myelodysplastic syndromes (Abstract #238), Berlin, 2013

Could ehrlichial infection cause some of the changes associated with leukemia, myelodysplastic diseases and autoimmune disorders, and offer antibiotic treatment options?, Kallick, C.A.; Friedman, D.A., Nyindo, M.; Medical hypotheses (2015) 891-893, Elsevier Ltd.: "…We reference here 3 leukaemia patients with direct or indirect evidence of Ehrlichia/Anaplasma (EA) infection….Though they did not survive, their condition improved dramatically for a time, suggesting Rifampin provided some therapeutic benefit…"

Members of the Ehrlichia genus are gram-negative, rod shaped bacteria that live inside white blood cells



Ehrlichia chaffeensis primarily infects mononuclear leukocytes (predominantly monocytes and macrophages),



The pathogen that causes human granulocytic ehrlichiosis (HGE) (Anaplasmosis) primarily infects granulocytes (neutrophils and rarely eosinophils).

Ehrlichia associated with myelodysplastic disease and leukaemia

ELSEVIER

Medical Hypotheses

Volume 85, Issue 6, December 2015, Pages 891-893

Could ehrlichial infection cause some of the changes associated with leukemia, myelodysplastic diseases and autoimmune disorders, and offer antibiotic treatment options?

Charles A. Kallick[a], Daniel A. Friedman[b], Mramba B.A. Nyindo[c]

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https://doi.org/10.1016/j.mehy.2015.09.015

Abstract

We hypothesize that a large group of medical conditions of unknown etiology including leukemia, multiple myeloma, myelodysplastic and autoimmune disorders, may be associated with or caused by an obscure group of intracellular obligate parasitic bacteria named Ehrlichia/Anaplasma (EA). Ensconced in the stem cells of the bone marrow, EA may disrupt the normal development and function of many of the cells of immunity, manifesting itself as different syndromes. Recent studies of the activity of EA suggest direct effects on the immune system consistent with the manifestations of leukemia. We reference here three leukemia patients with direct or indirect evidence of EA infection. Moreover, EA have been

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"Recent studies of the activity of EA [Ehrlichia/Anaplasma] suggest direct effects on the immune system consistent with the manifestations of leukemia"

"It is further hypothesized, moreover, that treatment of leukemia with antibiotics effective against EA would also result in beneficial impact. This has been tried. The results, cited below, hint at proof of EA infection as a cause of leukemia as well as a potentially important course of treatment."

Ehrlichia and leukaemia

Hypothesis: ehrlichial infection and leukemia

Jump to Section Go

Diseases of the immune system broadly described by the term leukemia include acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL) and chronic myeloid leukemia (CML). The causes of these leukemic syndromes are unknown though many genetic changes have been associated with some forms.

In leukemia we observe the overproduction of cells needed for immune system function, accompanied by large numbers of immature and dysfunctional cells of immunity (termed blasts) that are inappropriately released into the circulation. Something unknown is causing these blasts to fail to function as expected and accumulate in the system of the patient.

The Ehrlichia/Anaplasma (EA) are a family of obligate intracellular parasitic bacteria that infect leukocytes. They have been recognized as human pathogens for a variety of medical conditions [[1], [2]]. EA can alter the DNA of their host cell during its division, as discussed below. Interference with the normal progression of marrow cell development may facilitate the survival of the bacteria in their host leukocytes, by suppressing apoptosis and could also cause a cascade of subsequent immune system failures.

The EA are a Chlamydia, which have different reproductive methods than many other invasive bacterial pathogens. A study of *Ehrlichia Chaffeensis* infection in a human monocyte cell line demonstrated the ability of EA to alter host genes during transcription (transcriptomic effects) [3]. These effects included suppression of apoptosis, a primary defensive activity of intracellular pathogens regulating cell differentiation, and others essential for survival of the obligatory intracellular parasite. A culture of *Anaplasma phagocytophilum* was induced to grow in human immune system cells and produced most of the changes seen in leukemia [4].

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Source: http://dx.doi.org/10.1016/j.mehy.2015.09.015

Ehrlichia and bone marrow diseases

Format: Abstract Send to

Med Hypotheses. 2011 Sep;77(3):374-9. doi: 10.1016/j.mehy.2011.05.019. Epub 2011 Jun 12.

Ehrlichia and bone marrow cells: could Ehrlichial infection explain the unsuspected etiology of some diseases of the immune system?

Kallick CA[1].

Author information

Abstract

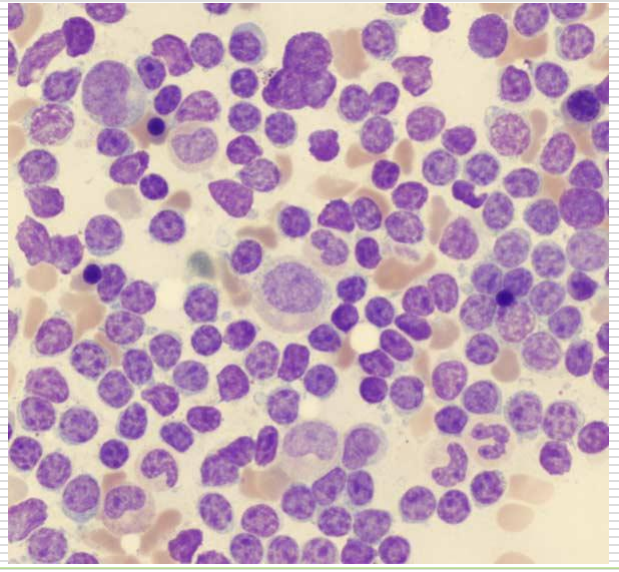
A large group of diseases of unknown etiology, including leukemia, systemic lupus erythematosus, myelodysplastic disease, multiple sclerosis, amyotrophic lateral sclerosis, and rheumatoid arthritis, all present with some elements of immune system disturbance. The Ehrlichia/anaplasma (EA) are an obscure group of obligate parasitic intracellular pathogens that excrete intracellularly a substance called host transcriptional protein, which can alter transcription in cell division. Infection with EA may lead to changes in transcription in proliferating cells, such as those in the marrow, and alter the biology of the products such as T and B cells. Normally 60% of B cells produced in the marrow may be self reactive, but are eliminated before release from the marrow. Changes in transcription could allow self reactive cells to escape into the peripheral circulation and injure normal tissue, creating the dysfunctions which characterize the different immune system diseases and give them their separate identities. A number of studies previously published, and new information presented here, suggest that EA infections may be an underlying, undiagnosed cause for these and other immune system diseases. This hypothesis, long overlooked, has never been subjected to adequate, rigorous study sufficient to prove or disprove its truth. If so, patients may be treated with antibiotics, and marrow transplant manipulations already used in treatment of diseases such as lupus and leukemia may become more effective.

Myelodysplastic syndrome/Leukaemia: Laboratory tests

1. Ehrlichia/Anaplasma EliSpot
2. Ehrlichia IgG/IgM antibodies
3. Anaplasma IgG/IgM antibodies

MGUS (Monoclonal Gammopathy of Undetermined Significance)

Monoclonal gammopathy of undetermined significance (MGUS) is a condition in which an abnormal protein — known as monoclonal protein or M protein — is in your blood. ... MGUS can progress over years to other disorders, including some forms of blood cancer



MGUS (Monoclonal Gammopathy of Undetermined Significance) associated with infections

TABLE 3. **Top 20 Previously Unpublished Associations Among Olmsted County, Minnesota, Residents With MGUS, by Significance in Systematic Analysis of Diagnostic Codes**[a]

Description	Positive MGUS cases	Case rate[b]	Positive controls	Control rate[b]	Relative risk (95% CI)	*P* value[c]
Hyperlipidemia[d]	247	2205.1	8653	3321.7	0.7 (0.6-0.8)	<.001
Uterus retroversion	6	347.9	36	32.6	10.7 (4.5-25.4)	<.001
Chalazion	44	336.9	695	170.7	1.97 (1.5-2.7)	<.001
Clavicle fracture	4	27.8	7	1.7	15.9 (4.6-55.9)	<.001
Upper respiratory bacterial infection	4	30.4	11	2.4	12.6 (3.9-40.5)	<.001
Small intestine diverticulum	4	32.6	5	1.8	18.0 (4.7-68.6)	<.001
Acute depression	13	183.2	172	54.4	3.4 (1.9-5.9)	<.001
Vitreous degeneration	6	47.2	31	7.3	6.5 (2.7-15.7)	<.001
Aphakic detachment	3	22.9	3	0.8	29.5 (5.8-150.4)	<.001
Vertebral fracture	26	301.8	217	130.8	2.3 (1.5-3.5)	<.001
Ventricle hypertrophy due to hypertension	9	69.8	54	17.7	3.9 (1.9-8.0)	<.001
Spontaneous bacterial peritonitis	3	20.8	5	1.3	16.7 (3.9-72.3)	<.001
Peritoneum cyst	4	28.3	14	3.2	8.8 (2.8-27.2)	<.001
Group I hypertension	16	119.4	188	44.5	2.7 (1.6-4.5)	<.001
Sural phlebitis	4	29.3	13	3.3	8.8 (2.8-27.3)	<.001
Mycobacterium infection	4	29.3	11	3.2	9.1 (2.8-29.0)	<.001
Hypercholesterolemia	68	501.2	2835	782.4	0.6 (0.5-0.8)	<.001
Sigmoid diverticulum with diverticulitis	10	71.1	80	21.5	3.3 (1.7-6.4)	<.001
Hyperglycemia	48	386.9	1871	647.7	0.6 (0.5-0.8)	<.001
Subconjunctival hematoma	3	21.6	8	1.9	11.2 (2.9-43.0)	<.001

[a] CI = confidence interval; MGUS = monoclonal gammopathy of undetermined significance.
[b] Rates per 100,000 person-years; age and sex adjusted.
[c] Unadjusted *P* values are reported.
[d] *P* value was significant after Bonferroni correction for 16,062 comparisons.

Mod. nach Bida JP et al., Mayo Clin Proc 2009; 84: 685-693

MGUS - Bartonella

Am J Hematol. 2006 Feb;81(2):115-7.

Transient monoclonal gammopathy in a patient with Bartonella quintana endocarditis.

Sève P[1], Turner R, Stankovic K, Perard L, Broussolle C.

Author information

Abstract

Monoclonal gammopathy has been reported rarely in association with infectious diseases. Viral infection has been the most frequently reported. We report a case of Bartonella quintana endocarditis in a 45-year-old homeless male associated with a monoclonal IgG kappa gammopathy. The gammopathy disappeared after 8 months of antibiotics while the Bartonella antibody titre was decreasing. This correlation suggests a causative role for B. quintana for the monoclonal gammopathy. To the best of our knowledge, this the first report of monoclonal gammopathy in the course of B. quintana infection.

PMID: 16432867 DOI: 10.1002/ajh.20499

[Indexed for MEDLINE] Free full text

"This correlation suggests a causative role for B. quintana for the monoclonal gammopathy."

"The gammopathy disappeared after 8 months of antibiotics"

Source: Am J Hematol. 2006 Feb;81(2):115-7

MGUS and axonal neuropathy

Axonal neuropathy associated with monoclonal gammopathy of undetermined significance FREE

PDF

Kenneth C Gorson, Allan H Ropper

Author affiliations +

Abstract

OBJECTIVE The neuropathy associated with monoclonal gammopathy of undetermined significance (MGUS) is typically a predominantly demyelinating process that may have additional features of axonal degeneration. Sixteen patients with MGUS and a pure or predominantly axonal neuropathy are reported and compared with 20 consecutive patients with demyelinating neuropathy and MGUS who were seen during the same period.

METHODS Retrospective review of a consecutive series of patients with neuropathy and MGUS evaluated during a five year period.

RESULTS The axonal group had mild, symmetric, slowly progressive, predominantly sensory neuropathy, usually limited to the legs. There were no differences in the age of onset or duration of symptoms at the time of presentation, initial symptoms, or the severity of weakness between the axonal and demyelinating cases. However, the axonal process was associated with less vibration and proprioceptive loss, did not include leg ataxia (present in 55% of patients with demyelinating type), less often had generalised areflexia (19% *v* 70%), IgM gammopathy (19% *v* 80%), and anti-MAG antibodies (0% *v* 40%), and had lower CSF protein concentrations (mean, 49 *v* 100 mg/dl). The illness was also generally milder with less disability (mean Rankin score 2.1 *v* 2.8). Fewer patients with axonal neuropathy improved with immunomodulating therapy (27% *v* 75%).

CONCLUSION There is an axonal neuropathy associated with MGUS that is clinically and electrophysiologically distinct from the more typical demyelinating pattern.

"There is considerable pathological evidence suggesting that the neuropathy associated with MGUS is primarily demyelinating"

"In the late period of Lyme disease demyelinating involvement of central nervous system can develop and MS can be erroneously diagnosed."

Med Hypotheses. 2007;69(1):117-9. Epub 2007 Jan 2.
Lyme borreliosis and multiple sclerosis are associated with primary effusion lymphoma

Monoclonal gammopathy of unknown significance (MGUS): Laboratory tests

1. Borrelia EliSpot + Tickplex Basic + CD57 cells
2. Bartonella EliSpot

… and consider the tests recommended for MS-type syndromes in cases accompanied by axonal neuropathy:

1. Chlamydia pneumonia Elispot + IgG/IgA antibodies
2. Mycoplasma pneumoniae EliSPot and IgG/IgA antibodies
3. Bartonella EliSpot
4. Coxsackie Virus IgG/IgA antibodies
5. EBV EliSpot
6. CMV EliSpot
7. HHV6 EliSpot

Ehrlichiosis can also mimic T-cell lymphoma

Ehrlichiosis Mimicking T-Cell Lymphoma/Leukemia.

Ashok Malani, Robert Weigand, Vicram Gupta, Lawrence Hertzberg and Gautam Rangineni

Blood 2005 106:4343;

Article | Figures & Data | Info & Metrics | e-Letters

Abstract

Immunophenotyping by flow cytometry has revolutinized the diagnosis of blood cell disorders such as leukemias and lymphomas and is now commonly used in diagnosis and prognosis of such patients. We describe a case of human ehrlichiosis mimicking T-cell lymphoma/leukemia based on flow cytometry of bone marrow cells and confirmed by T-cell receptor gene rearrangement (TCR) by polymerase chain reaction (PCR). Treatment with doxycycline reversed these findings. A 20-year-old, Amish female presented with fatigue, fever, chills, sweating, low back pain, and lower abdominal pain for 2 days. She admitted to multiple bites from ticks 2 weeks prior to presentation and also reported having numerous animals such as cats, dogs, cows, goats, horses at her farm where she lived. Clinical exam was significant for fever of 101.4 F, heart rate of 118/min, BP of 80/60 mm Hg and a distended urinary bladder which was treated by catheter drainage. Relevant laboratory tests are shown in table 1.

Hemoglobin	9.7	12-16 gm/dl
WBC	0.8	4-10.8

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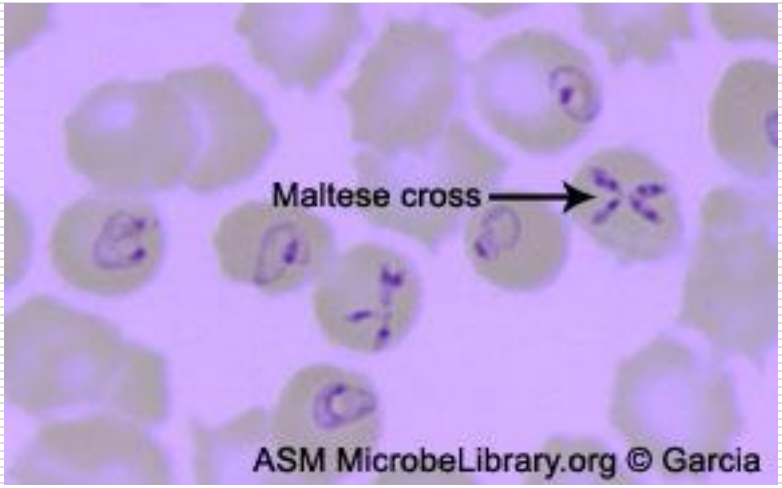
Issue: 11
Pages: 4343
DOI: https://doi.org/

Babesia and red blood cells

Babesia is a parasite that infects red blood cells causing a disease known as **babesiosis**

Erythrocytes carry oxygen throughout the body. Damage to a large number of these cells can decrease the level of oxygen in the blood

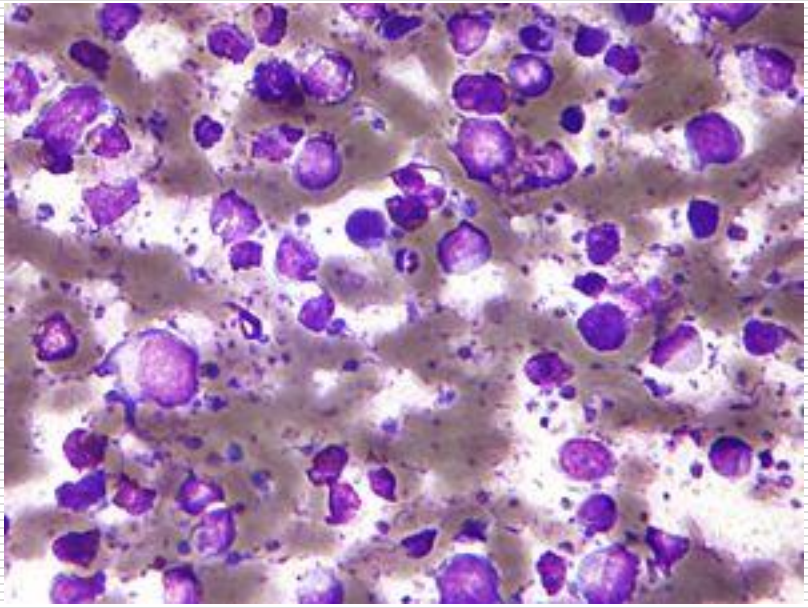


Babesiosis, according to the CDC, can cause low and unstable blood pressure, severe hemolytic anemia (hemolysis), a very low platelet count (thrombocytopenia), disseminated intravascular coagulation (DIC, or consumptive coagulopathy), which can lead to the above-mentioned blood clots and bleeding

"**Very high D-Dimer and thrombin-antithrombin complex formation (TAT) blood levels were found in our *Babesia* patients**"
http://www.townsendletter.com/July2015/babesia0715.html

Lymphomas

Lymphomas are "blood cancers" in the lymph nodes._



Non-Hodgkin lymphoma (NHL) is a group of blood cancers that includes all types of lymphoma except Hodgkin's lymphomas

It comes in the form of
B-cell lymphoma and T-cell lymphoma

Babesia and B-cell lymphoma

Infect Dis Clin North Am. Author manuscript; available in PMC 2014 Apr 24.
Published in final edited form as:
Infect Dis Clin North Am. 2008 Sep; 22(3): 469–ix.
doi: 10.1016/j.idc.2008.03.010

PMCID: PMC3998201
NIHMSID: NIHMS70263

Human Babesiosis

Edouard Vannier, PhD,[a] Benjamin E. Gewurz, MD, PhD,[b] and Peter J. Krause, MD[c,d]

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Introduction

Go to:

Human babesiosis is an emerging tick-borne infectious disease caused by protozoa of the genus *Babesia* that are obligate parasites of red blood cells. Long recognized as pathogens imposing a significant health burden on domesticated animals, *Babesia* spp. increasingly have been identified over the last 50 years as a cause of infection in people throughout the world.

The first reference to babesiosis is probably in Exodus 9:3, which describes the plague visited upon the cattle of Pharaoh Rameses II. Viktor Babes, a Hungarian pathologist wh... hemoglobinuria in cattle grazing in the Danube region of Romania, was... microorganism residing in red blood cells.[1] Shortly thereafter, Smith ... organism in Texas cattle.[2] Named *Pyrosoma bigeminum* after its pear... recognized as *Babesia bigemina*. The cattle tick, *Boophilus annulatus*, was identified as the vector for transmission of Texas cattle fever. By making this seminal observation, Smith and Kilborne established the concept that hematophagous arthropods can transmit an infectious agent to vertebrate hosts. More than 100 species of babesia subsequently have been identified in wild and domestic animals.[3]

"Interestingly, the majority of case patients in the study had underlying B-cell lymphoma"

Borrelia and non-Hodgkin lymphoma

CLINICAL TRIALS AND OBSERVATIONS

Borrelia infection and risk of non-Hodgkin lymphoma

Claudia Schöllkopf,[1] Mads Melbye,[1] Lars Munksgaard,[2] Karin Ekström Smedby,[3] Klaus Rostgaard,[1] Bengt Glimelius,[4,5] Ellen T. Chang,[6,7] Göran Roos,[8] Mads Hansen,[2] Hans-Olov Adami,[3,9] and Henrik Hjalgrim[1]

[1]Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark; [2]Department of Hematology, Rigshospitalet, C
Hospital, Copenhagen, Denmark; [3]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; [4]D
and Oncology, Karolinska Institutet, Stockholm, Sweden; [5]Department of Oncology, Radiology and Clinical Immunology, Uppsala Unive
[6]Northern California Cancer Center, Fremont; [7]Department of Health Research and Policy, Stanford University School of Medicine, CA;
Pathology, Norrlands University Hospital, Umeå, Sweden; and [9]Department of Epidemiology, Harvard School of Public Health, Boston,

**Reports of the presence of *Borrelia burgdorferi* DNA in malignant lymphomas have raised the hypothesis that infection with *B burgdorferi* may be causally related to non-Hodgkin lymphoma (NHL) development. We conducted a Danish-Swedish case-control study including 3055 NHL patients and 3187 population controls. History of tick bite or *Borrelia* infection was ascertained through structured telephone interviews and through enzyme-linked immunosorbent assay serum analyses for antibodies against *B burgdorferi* in a subset of 1579 patients and 1358 controls. Statistical associations with risk of NHL, including histologic subtypes, were assessed by logistic regression. Overall risk of NHL was not associated with self-reported history of tick bite (odds ratio [OR] = 1.0; 95% confidence interval: 0.9-1.1), *Borrelia* infection (OR = 1.3 [0.96-1.8]) or the presence of anti-*Borrelia* antibodies (OR = 1.3 [0.9-2.0]). However, in analyses of NHL subtypes, self-reported history of *B burgdorferi* infection (OR = 2.5 [1.2-5.1]) and seropositivity for anti-*Borrelia* antibodies (OR = 3.6 [1.8-7.4]) were both associated with risk of mantle c
bly, this specific as
observed in persons
Borrelia infection
for anti-*Borrelia* ar
[2.0-8.9]). Our observa
viously unreported association between *B burgdorferi* infection and risk of mantle cell lymphoma. (Blood. 2008;111: 5524-5529)**

Introduction

In recent years, a growing number of infectious agents have been linked to non-Hodgkin lymphoma (NHL), including, for example, *Chlamydia psittaci,* hepatitis C virus, *Campylobacter jejuni,* and *Helicobacter pylori.*[1-4] While each of these infectious agents accounts only for a small proportion of the total number of NHL cases, the observed associations are important because they have clinical and therapeutic implications and provide novel insight into the mechanisms that govern lymphoma development.

Patients with symptomatic infection with the spirochete *Borrelia burgdorferi* display characteristic manifestations that may include skin rash, arthritis, and neurologic deficits, a clinical

Moreover, regression of lymphomas upon treatment of the *Borrelia* infection has also been reported.[13,14]

While the evidence that *B burgdorferi* may be implicated in development of cutaneous B-cell lymphomas is considerable, the question remains if the association may also pertain to noncutaneous lymphomas. Infection with *B burgdorferi* is indeed not limited to the skin, but, as reflected by its wide range of clinical manifestations, also disseminates to other regions including, presumably, the lymphoid tissues.[15] It is, therefore, of interest that we recently demonstrated the presence of *B burgdorferi* DNA within the malignant lesions of 2 patients with nodal B-cell lymphoma.[16]

Inspired by this body of evidence, we investigated the hypoth-

"Reports of the presence of Borrelia burgdorferi DNA in malignant lymphomas have raised the hypothesis that infection with B burgdorferi may be causally related to non-Hodgkin lymphoma (NHL) development"

"Moreover, regression of lymphomas upon treatment of the Borrelia infection has also been reported"

Source: Blood. 2008 Jun 15; 111(12): 5524–5529 https://ann-clinmicrob.biomedcentral.com/articles/10.1186/s12941-017-0179-z

Bartonella and lymphoma

Format: Abstract ▾ Send to ▾

Scand J Infect Dis. 2001;33(12):935-6.

Bartonella henselae infection mimicking a splenic lymphoma.

Ghez D[1], Bernard L, Bayou E, Bani-Sadr F, Vallée C, Perronne C.

⊕ Author information

Abstract

We report a Bartonella henselae infection in a 40-y-old patient who presented with fever, weight loss, night sweats, elevated lactate dehydrogenase and multinodular splenomegaly with multiple abdominal lymphadenopathies. Splenic cat-scratch disease is an exceptional diagnosis in adults and can easily be mistaken for a splenic lymphoma, thereby leading to an unnecessary splenectomy.

PMID: 11868771

[Indexed for MEDLINE]

"The spleen is a vital organ in clearing erythrocytes …. The role of the spleen can be illustrated by the mechanism of sequestration, since the parasitized erythrocytes lack the deformability needed to transit the splenic sinusoids and are therefore sequestered within the spleen by resident macrophages"

Source: https://ann-clinmicrob.biomedcentral.com/articles/10.1186/s12941-017-0179-z

B-Cell Non-Hodgkin's Lymphoma: Coxiella burnetii

- **B-Cell Non-Hodgkin's Lymphoma linked to Coxiella burnetii. Melenotte C. et al. www.bloodjournal.org Blood First Edition Paper November 12, 2015:**

  "Coxiella burnetii is associated with an increased risk of lymphoma, its presence in the tumor microenvironment may favor lymphomagenesis."

  "Lymphoma has to be considered in patients with Qfever and lymphoid disorders, especially those with persistent focalized infections."

B-Cell Non Hodgkin's Lymphoma: Coxiella burnetii

Q fever is a worldwide disease with acute and chronic stages caused by the bacteria ***Coxiella burnetii***.

Cattle, sheep, and goats are the primary reservoirs. Coxiella burnetii are excreted in milk, urine, and feces of infected animals.

Infection of humans usually occurs by inhalation of Coxiella burnetii from air that contains airborne barnyard dust contaminated by dried placental material, birth fluids, and excreta of infected animals.

Other modes of transmission to humans, **including tick bites**, and ingestion of unpasteurized milk or dairy products.

Coxiella/Q fever and B-cell lymphoma

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Blood. 2016 Jan 7; 127(1): 10–11.
doi: 10.1182/blood-2015-11-677203
PMCID: PMC4705601
Lymphoid Neoplasia

Identifying risk factors for B-cell lymphoma

Christopher R. Flowers[1] and Christine F. Skibola[2]

Author information ► Copyright and License information ►

See "B-cell non-Hodgkin lymphoma linked to Coxiella burnetii." in volume 127 on page 113.

This is one of the first studies to focus on *Coxiella burnetii* (the infectious agent associated with Q fever) as an inciting factor for lymphomas. Building on the identification of an incident case, the authors examined the incidence of lymphoma among individuals within a cohort of patients with Q fever. These analyses provide clinically meaningful insights that may aid in the identification of a novel risk factor for diffuse large B-cell lymphoma (DLBCL) and other B-cell NHLs and support the development of a comprehensive understanding of factors associated with lymphoma incidence. Utilizing a French National Referral Center for Q fever database of 1468 consecutive patients diagnosed from 2004 to 2014, and accounting for differences in age and sex distribution between the Q fever cohort and the general French population, the authors identified an increase in the incidence of DLBCL and follicular lymphoma (FL) in individuals who had Q fever compared with the general population, with standardized incidence rates of 25.4 (95% confidence interval [CI], 11.4-56.4) and 6.7 (95% CI, 0.9-47.9), respectively. Moreover, a diagnosis of Q fever with a persistent focal infection was noted to have a greater risk of lymphoma with a hazard ratio of 9 over the period of observation. For these analyses, acute Q fever was defined by the association of clinical symptoms (fever, hepatitis, and/or pneumonia) with the serological criteria of a phase 2 immunoglobulin G (IgG) titer ≥200 and a phase 2 IgM titer ≥50, seroconversion or a positive polymerase chain reaction (PCR), and no endocarditis. Supporting these epidemiological data were findings that interleukin-10 production was significantly increased in patients with lymphoma, particularly those with Q fever.

Link between Coxiella/Q fever and leukaemia/lymphoma

3 February 2016

Revisiting the Link between Coxiella Infection and Leukemic/Lymphoma Transformation

Han Sang Kim, Medical Oncologist Department of Pharmacology, Brain Korea 21 PLUS Project for Medical Science, Yonsei University College of Medicine, Seoul, Korea

Other Contributors:

Won Young Lee, Professor Emeritus

We have read with great interest the recent article published by Melenotte et al.1 In 1993, we reported that Coxiella burnetti infection causes hairy cell transformation.2 In our research, all three strains of Coxiella induced hairy cell transformation in vitro in average of 20 days after inoculation, and the half (6 of 12) of newly established hairy cells from the blood samples of patients with hematologic disorders (hairy cell leukemia and polymorphic reticulosis) were parasitized with Coxiella burnetti.2

An obligate intracellular pathogen Coxiella replicates within acidic, highly proteolytic, and oxidative lysosome-like vacuole known as Coxiella-containing vacuole (CCV). More than 120 Coxiella effector proteins, secreted by Dot/Icm (defect in organelle trafficking/intracellular multiplication) system from CCV into the host cell, (i) contribute to anti-apoptotic effects by inhibition of cytochrome c release from mitochondria, (ii) activate pro-survival kinases (e.g., AKT and ERK1/2) and mitogen-activated protein (MAP) kinase signaling, (iii) induce filamentous-actin cytoskeleton reorganization by Src-related kinase activation, and (iv) evade immune surveillance through lipopolysaccharide, demonstrating a potential role for tumorigenesis.3 Although Coxiella invades both phagocytic cells (monocytes and macrophages) and non-phagocytic cells (epithelial and endothelial cells) and Coxiella can bind to macrophages via αVβ3 integrin as the specific receptor, it rem...

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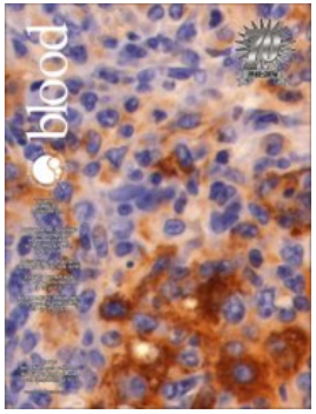

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DOI: https://doi.org/10.1182/blood-2015-04-639617

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B-cell Non-Hodgkin's Lymphoma: Suggested laboratory tests (of course compare with patient history and symptoms)

1. EBV EliSpot
2. EBV antibodies
3. CMV EliSpot
4. CMV antibodies
5. Coxiella burnetii IgG/IgM antibodies (Q Fever)
6. Ehrlichia/Anaplasma EliSpot
7. Borrelia EliSpot
8. CD57 cells + Tickplex Basic

Involvement of viral co-infections in cancer is well documented, too

E.g., Herpes viruses EBV and CMV and a number of haematological cancers, e.g., Non-Hodgkin's B-cell lymphoma

Epstein Barr virus

Epstein–Barr virus–associated B–cell non–Hodgkin lymphoma following treatment of hairy cell leukemia with cladribine

Georg Lenz, Alexander Golf, Thomas Rüdiger, Wolfgang Hiddemann and Torsten Haferlach

Blood 2003 102:3457–3458; doi: https://doi.org/10.1182/blood–2003–07–2494

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Epstein–Barr virus (EBV) is a tumorigenic herpes virus, which is as
several human hematologic neoplasias such as Burkitt lymphoma
and posttransplantation lymphoproliferative disease (PTLD). EBV–
lymphoproliferative disease represents a broad spectrum, ranging
disorders to malignant non–Hodgkin lymphomas occurring mainl
of immunodeficiency. However, its acute development after conve
chemotherapy as treatment for another malignancy is a rare findi

We report a case of acute EBV–associated B–cell diffuse large–cell
developing shortly after successful treatment of relapsed hairy ce
1998, a 46–year–old patient presented with splenomegaly, leukocytopenia, and thrombocytopenia. The peripheral blood smear demonstrated atypically appearing lymphocytes, resembling hairy cells. The bone marrow biopsy confirmed the diagnosis of hairy cell leukemia by May–Grunwald–Giemsa (MGG) staining, alkaline phosphatase antialkaline phosphatase (APAAP), and immunophenotyping with 85%

Epstein-Barr virus (EBV) is a tumorigenic herpes virus, which is associated with several human hematologic neoplasias such as Burkitt lymphoma, Hodgkin disease, and posttransplantation lymphoproliferative disease (PTLD)

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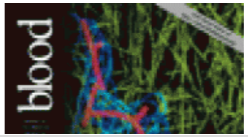

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Issue: 9
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*Source: * Ramesh G et al. Interaction of the Lyme Disease Spirochete Borrelia burgdorferi with Brain Parenchyma Elicits Inflammatory Mediators from Glial Cells as Well as Glial and Neuronal Apoptosis. Am J Pathol. 2008 Nov; 173(5): 1415–1427*

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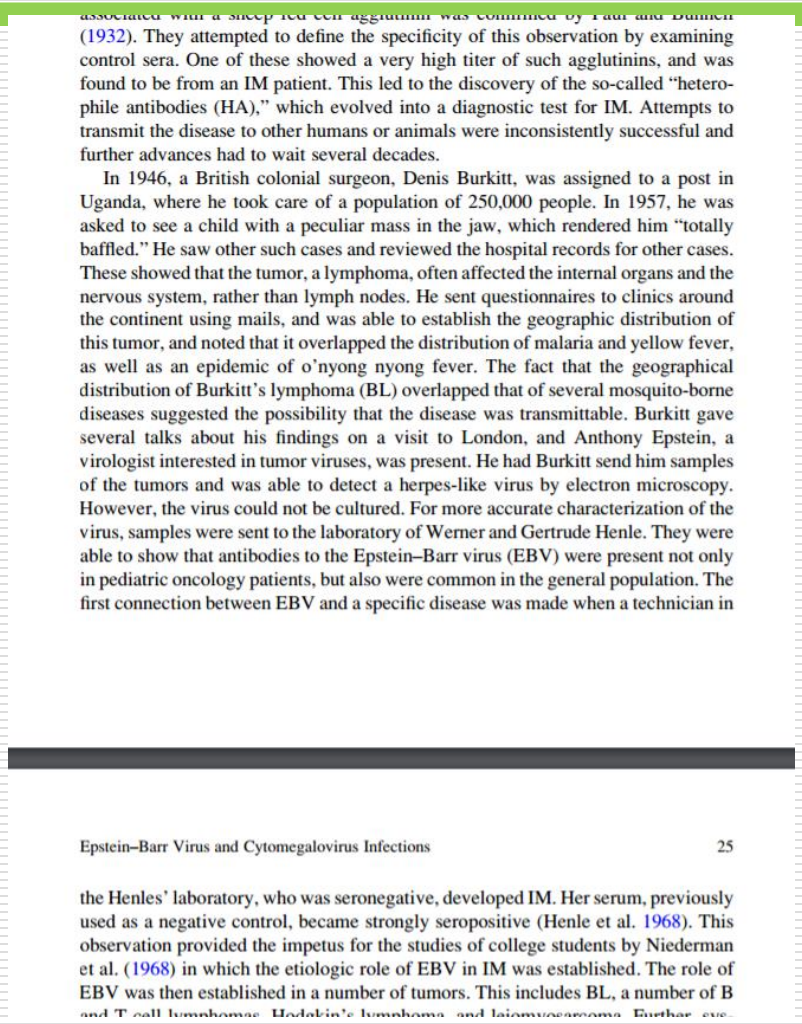
DIAGNOSING TICK-BORNE DISEASES

B-Cell Non-Hodgkin's Lymphoma: EBV/CMV

- **Epstein Barr Virus-associated Non-Hodgkin's lymphoma of B-cell origin, Hodgkin's disease, acute leukemia, and systemic lupus erythematosus: a serologic and molecular analysis, Mitarnun W, Pradutkanchana J, Takao S, Saechan V, Suwiwat S, Ishida T** http://www.ncbi.nlm.nih.gov/pubmed/12188384
- **EBV-Associated Lymphoproliferative Disorders: Classification and Treatment, Carbone A, Annunziata G, Dotti, G, The oncologist** 1083-7159/2008
- **Cytomegalovirus infection in patients with lymphoma: an important cause of morbidity and mortality. Torres HA, Kontoyiannis DP, Aguilera EA, Younes A, Luna MA, Tarrand JJ, Nogueras GM, Raad II, Chemaly RF. Clin. Lymphoma Myeloma, 2006 Mar;6(5): 393-8**

History of the discovery of EBV points to its tumorigenic origin



associated with a sheep red cell agglutinin was confirmed by Paul and Bunnell (1932). They attempted to define the specificity of this observation by examining control sera. One of these showed a very high titer of such agglutinins, and was found to be from an IM patient. This led to the discovery of the so-called "heterophile antibodies (HA)," which evolved into a diagnostic test for IM. Attempts to transmit the disease to other humans or animals were inconsistently successful and further advances had to wait several decades.

In 1946, a British colonial surgeon, Denis Burkitt, was assigned to a post in Uganda, where he took care of a population of 250,000 people. In 1957, he was asked to see a child with a peculiar mass in the jaw, which rendered him "totally baffled." He saw other such cases and reviewed the hospital records for other cases. These showed that the tumor, a lymphoma, often affected the internal organs and the nervous system, rather than lymph nodes. He sent questionnaires to clinics around the continent using mails, and was able to establish the geographic distribution of this tumor, and noted that it overlapped the distribution of malaria and yellow fever, as well as an epidemic of o'nyong nyong fever. The fact that the geographical distribution of Burkitt's lymphoma (BL) overlapped that of several mosquito-borne diseases suggested the possibility that the disease was transmittable. Burkitt gave several talks about his findings on a visit to London, and Anthony Epstein, a virologist interested in tumor viruses, was present. He had Burkitt send him samples of the tumors and was able to detect a herpes-like virus by electron microscopy. However, the virus could not be cultured. For more accurate characterization of the virus, samples were sent to the laboratory of Werner and Gertrude Henle. They were able to show that antibodies to the Epstein–Barr virus (EBV) were present not only in pediatric oncology patients, but also were common in the general population. The first connection between EBV and a specific disease was made when a technician in

Epstein–Barr Virus and Cytomegalovirus Infections 25

the Henles' laboratory, who was seronegative, developed IM. Her serum, previously used as a negative control, became strongly seropositive (Henle et al. 1968). This observation provided the impetus for the studies of college students by Niederman et al. (1968) in which the etiologic role of EBV in IM was established. The role of EBV was then established in a number of tumors. This includes BL, a number of B and T cell lymphomas, Hodgkin's lymphoma, and leiomyosarcoma. Further, evi-

"The fact that the geographical distribution of Burkitt's lymphoma (BL) overlapped that of several mosquito-borne diseases suggested the possibility that the disease was transmittable. Burkitt gave several talks about his findings on a visit to London, and Anthony Epstein, a virologist interested in tumor viruses, was present. He had Burkitt send him samples of the tumors and was able to detect a herpes-like virus by electron microscopy."

Source: Epstein-Barr Virus and Cytomegalovirus infections Alex Tselis

EBV/CMV and tumours

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"The role of EBV was then established in a number of tumors"

Source: Epstein-Barr Virus and Cytomegalovirus infections Alex Tselis

EBV: Latency antigens and types associated with various cancers

Table 1 Latency antigens and types

Latency type	Latency antigens						
	EBER	EBNA-1	EBNA-2	EBNA-3	LMP-1	LMP-2	BARTs
1	+	+	–	–	–	–	+
2	+	+	–	–	+	+	+
3	+	+	+	+	+	+	+
Other	+	+/–	–	–	–	+	+/–

Latency types	
Latency 1	Burkitt's lymphoma
Latency 2	Nasopharyngeal carcinoma, Hodgkin's disease
Latency 3	Infectious mononucleosis, lymphoproliferative disease
Other	Perpheral blood B lymphocytes

EBER Epstein–Barr virus-encoded RNA, *EBNA* Epstein–Barr nuclear antigen, *LMP* Latent membrane protein, *BART* BamHI A rightward transcripts

The pathogenesis of encephalitis (or meningitis or hepatitis or other focal visceral involvement) is not completely clear and there are several possibilities, which are not mutually exclusive. First, EBV may affect neurons (or other neural cells or endothelium) directly (Jones et al. 1995). There have been a few scattered reports of neurons and glial cells staining with EBV antigens, although there is not much detail (Biebl et al. 2009). In some patients with EBV encephalitis, as well as some with primary CNS lymphoma, lytic EBV mRNA was detected in the CSF, suggesting lytic replication of EBV in the brain in addition to latent replication (Weinberg et al. 2002a). Secondly, EBV-infected B cells are in an activated state and elaborate several proinflammatory cytokines, which can cause injury of the surrounding parenchyma (Foss et al. 1994). This injury is not necessarily irreversible. Third, EBV-infected B cells are actively attacked by EBV-specific cytotoxic T cells, and this can also injure the surrounding parenchyma. Finally, an acute disseminated encephalomyelitis can be triggered as in other viral infections.

Normally, EBV-infected B cells are suppressed (though not eliminated) by the immune system and lymphoproliferation can result during immunosuppression. In tissue culture in which T cells have been eliminated, B cells are immortalized and proliferate. In vivo, the B cell lymphoproliferation proceeds sequentially from polyclonal to oligoclonal to monoclonal, and evolves into a lymphoma. This can occur under circumstances of immunosuppression in transplant, chemotherapy, and AIDS patients as mentioned above. The lymphoproliferation can be accompanied by the elaboration of various cytokines, and a severe systemic illness resembling

"How EBV causes blood cancer", study, University of Sussex - report November 2016

Scientists reveal how a common virus triggers blood cancer

Scientists at the University of Sussex, trying to uncover how the common Epstein-Barr virus causes blood cancer in adults and children, have discovered how the virus takes control of two genes involved in cancer development so it can switch them on or off.

The research team, led by Professor Michelle West, set out to determine how the Epstein-Barr virus controls two genes; *MYC*, a gene known to drive cancer development when it is altered or switched on at high level and *BCL2L11*, a gene which normally triggers cell death to prevent cancer, but can be turned off by the virus.

With thanks to funding from the blood cancer charity Bloodwise, the scientists discovered that the virus controls the *MYC* and *BCL2L11* genes by hijacking 'enhancer' DNA regions which are situated far away from the genes. These enhancers act as 'control centres' and are able to contact and control genes from long distances by the looping out of the intervening stretches of DNA.

Professor Michelle West

Professor West's team found that Epstein-Barr virus turns on the *MYC* gene by increasing contacts between a specific set of enhancers and the gene. The scientists believe this may explain how the virus causes the changes to the *MYC* gene that are found in Burkitt's lymphoma.

The team also discovered new enhancers which control the *BCL2L11* gene. In this case, they found that Epstein-Barr virus stops these control centres from contacting the gene. Encouragingly the team have discovered that this blocking effect can be reversed by using a specific drug - paving the way for new treatments.

Professor West said: "This is a key step towards uncovering how this common virus which, affects thousands of people every year, causes blood cancer.

"It is now important to carry out further studies to c tell us more about how the virus drives lymphoma developmen ugs."

Dr Alasdair Rankin, Research Director at Bloodwis a, but we were never sure of the exact mechanisms. These e behaviour of genes that control cancer growth.

Professor West said: "This is a key step towards uncovering how this common virus which, affects thousands of people every year, causes blood cancer."

"By mapping out the complex genetic interactions that help lymphoma cells grow and survive, this research can guide the design of new treatments to target the disease. It may also help to identify those drugs currently used to treat other diseases that could be effective in treating these types of lymphoma."

Herpes viruses and blood cancers: Laboratory tests

1. EBV EliSpot
2. EBV antibodies
3. CMV EliSpot
4. CMV antibodies
5. Coxiella burnetii IgG/IgM antibodies (Q Fever)
6. Ehrlichia/Anaplasma EliSpot
7. Borrelia EliSpot
8. CD57 cells + Tickplex Basic

PART III: Lyme and infections in other syndromes

Case report: "Mixed dementia"

65-year old patient with ataxia in walking, fatigue, loss of memory and concentration, depressions, increasing disorientation, hypertension, panic attacks, helplessness, change of character since 2011. Patient remembers several tick bites before the start of the illness.

Feb. 3rd, 2013: University Hospital Munich: "Mixed dementia" with no findings in spinal fluid - "Exclusion of Neuroborreliosis"

Nov. 11th, 2014: Appointment in my office:

- Borrelia IgG-/IgM-specific antibodies detectable
- Borrelia EliSpot positive (Borrelia full antigen: SI 3)

Dec. 2015 / Jan. 2016: Treatment with oral antibiotic therapy: Cefuroxim, Clarythromycin and Metronidazol in a row

Case report: "Mixed dementia"

April 2nd, 2016) Increasing autonomy, significant improvement in ataxia und movement disorders, no panic attacks anymore

June 6th, 2016 Condition remains stable, following treatment for 12 weeks with oral Donta treatment scheme (Clarythromycin und Hydroxychloroquin)

Nov. 11th, 2016: Next consultation in my office:

- Borrelia antibodies IgG/IgM antibodies unchanged
- Borrelia EliSpot negative (SI <2)!

Patient is symptom-free!

Correct diagnosis: Chronic Neuroborreliosis with dementia-like symptoms

Acrodermatitis Chronica Atrophicans ACA and Alopecia

Int J Trichology. 2015 Jan-Mar; 7(1): 26–28.
doi: 10.4103/0974-7753.153454
PMCID: PMC4387695

Acute Diffuse and Total Alopecia of the Female Scalp Associated with *Borrelia*-Infection

Ekta K Bhardwaj and Ralph Michel Trüeb[1]

Renovia Medical Aesthetics and Hair Center, Manchester, England, UK
[1]Center for Dermatology and Hair Diseases, Zurich-Wallisellen, Switzerland
Address for correspondence: Prof. Dr. med. Ralph Michel Trüeb, Center for Dermatology and Hair Diseases, Bahnhofplatz 1A, CH-8304 Zurich-Wallisellen, Switzerland. E-mail: r.trueeb@derma-haarcenter.ch

Abstract Go to:

A case of acute diffuse and total alopecia of the female scalp associated with *Borrelia*-infection (acrodermatitis chronica atrophicans) is presented. Today, acute diffuse and total alopecia of the female scalp is recognized as a distinct variant of alopecia areata (AA) predominantly observed in women. Cases of AA have formerly been reported in association with infections. AA is understood to represent an organ-specific autoimmune disease of the hair follicle. It is conceivable that the antigenic stimulus provided by the infection may act as a trigger for alopecia. *Vice versa*, alopecia may act as a marker for detection of undiagnosed infection. Treatment of the patient with intravenous ceftriaxone led to the resolution of cutaneous borreliosis, and in addition to topical clobetasol foam to complete recovery of hair.

Keywords: *Borrelia* -infection, co-morbidity, diffuse alopecia areata

Researchers find that ancient Iceman's infection helps Lyme disease bone loss discovery

- Mitochondrial DNA analysis has shown that the **bacteria responsible for Lyme disease resided deep in Ötzi's bones**. Though he didn't die from complications of the disease, work from a team of scientists at the University of Toronto's Faculty of Dentistry now suggests that the 5,000-year-old man might have suffered from **bone loss as a result of his infection**.
- While scientists have long established a link between advanced Lyme disease and the development of osteoarthritis, until now **no one has systematically studied the effects of this disease on bones**.
- The bacteria were not only detectable in the bones of mice, **they were seen to cause significant bone loss in the longer bones, mere weeks after infection**.
- **In fact, the bone loss developed at a rapid rate, taking just four weeks to advance to osteopenia, a forerunner to the more severe form of bone loss disease, osteoporosis. The study found that the amount of bone loss directly correlated to the bacterial load found in the bones.** The more bacteria present, the greater the rate of bone loss.
- **The findings suggest that monitoring bone loss in human Lyme disease patients may be warranted, especially because bone loss is a significant risk factor for fractures later in life.**
- **"One of our main focuses right now is on the mechanism that induces the bone loss,"** said Tian Cornelia Tang, **Faculty of Dentistry**.
- **Cellular studies are currently underway to determine just how the bacteria interact with the bone building cells of the body, osteoblasts**, with the hope of finding new drug targets to combat not just the bacteria, but the newly discovered associated bone loss.
- **"We need to know how long the osteopenia lasts after bacterial infection, and whether it progresses to osteoporosis,"** added Moriarty.

Borrelia is associated with multiple autoimmune conditions

- Rheumatic fever, reactive arthritis, rheumatoid arthritis
- Molecular mimicry in neuroborreliosis
- Neuropathy
- Vasculitis
- Autoimmune thyroid disease/Hashimoto's
- Multiple sclerosis
- .....

Lyme arthritis: the first link between Borreliosis and autoimmune disease

The first indication that treatment-resistant Lyme borreliosis might be an autoimmune disease came from a study analysing MHC (major histocompatibility complex) II alleles (HLA-DR4) in patients with Lyme arthritis. MHC class II molecules play a critical role in activation of the immune system.

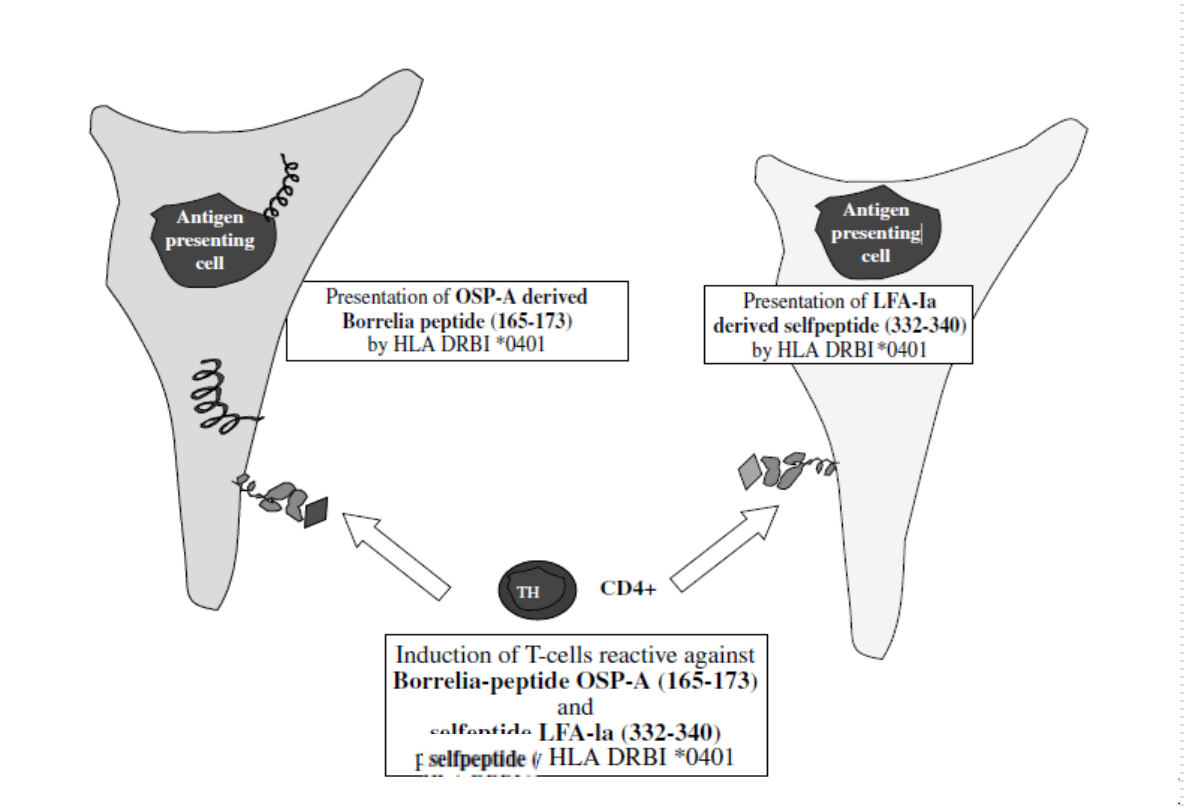
PX with chronic treatment-resistant Lyme arthritis have been found to have MHC II alleles associated with rheumatoid arthritis, partic. HLA-DRB1* 0401 and 0101 alleles.

These PX also develop anti-OspA antibodies correlating with the duration of their arthritis [138], suggesting that OspA may be involved in the autoimmune process.

Gross et al. suggested that LFA-1 (human leucocyte function-associated antigen 1) can serve as a cross-reactive autoantigen for OspA-reactive Th1 cells, leading to treatment-resistant Lyme arthritis. One potential explanation for antibiotic-resistant Lyme disease is thus generation of A/I directly or indirectly mediated by the pathogen and based on molecular mimicry.

Source: Kalish RA, Leong JM, Steere AC. Association of treatment-resistant chronic Lyme arthritis with HLA-DR4 and antibody reactivity to OspA and OspB of Borrelia burgdorferi. Infect Immun 1993; 61: 2774–2779; Gross DM, Forsthuber T, Tary-Lehmann M et al. Identification of LFA-1 as a candidate autoantigen in treatment-resistant Lyme arthritis. Science 1998; 281: 703–706.

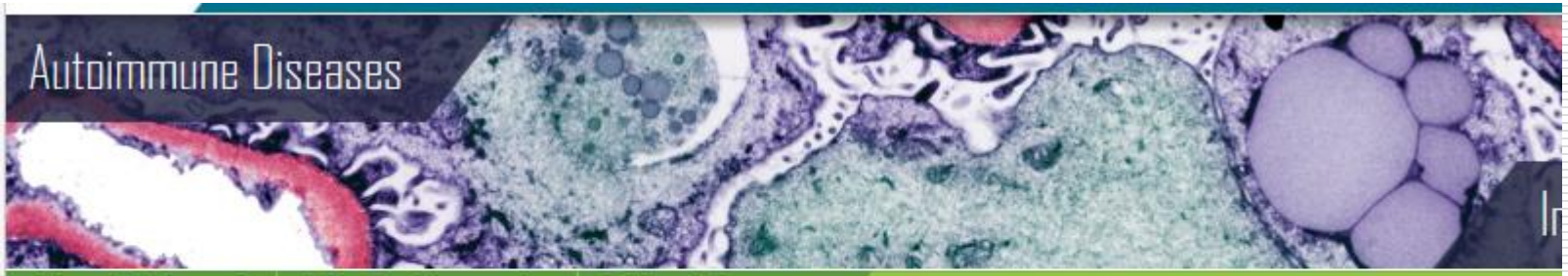
Intracellular persistence of Bb in synovial cells - molecular mimicry in Lyme arthritis



Antigen-presenting cells (monocytes, macrophages, dendritic cells and synovial fibroblasts) present peptides generated from borrelial OspA and host LFA-Ia (human leucocyte function-associated antigen 1), which induce a cross-reactive T-cell response

Source: Singh SK, Girschick HJ. Lyme borreliosis: from infection to autoimmunity. 2004. Clinical Microbiology and Infection (CMI), 10, 598–614

Infection-induced autoimmunity in rheumatic diseases



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Autoimmune Diseases
Volume 2012 (2012), Article ID 539282, 9 pages
http://dx.doi.org/10.1155/2012/539282

Review Article

Autoimmunity in Rheumatic Diseases Is Induced by Microbial Infections via Crossreactivity or Molecular Mimicry

Taha Rashid and Alan Ebringer

Analytical Sciences Group, Kings College London, 150 Stamford Street, London SE1 9NN, UK

Received 2 September 2011; Accepted 1 November 2011

Important to consider Borrelia in the differential diagnosis of rheumatoid arthritis

Clinical and Vaccine Immunology
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PMCID: PMC2168181

Serum Reactivity against *Borrelia burgdorferi* OspA in Patients with Rheumatoid Arthritis

Yu-Fan Hsieh,[1] Han-Wen Liu,[1] Tsai-Ching Hsu,[1] James C.-C. Wei,[2] Chien-Ming Shih,[3] Peter J. Krause,[4] and Gregory J. Tsay[1,2,*]

Author information ▶ Article notes ▶ Copyright and License information ▶

ABSTRACT

Go to:

Lyme arthritis and rheumatoid arthritis share common clinical features and synovial histology. It is unclear whether they also share similar pathogenesis. Previous studies have shown that the severity and duration of Lyme arthritis correlate directly with serum concentrations of antibody against outer surface protein A (OspA) of the causative pathogen *Borrelia burgdorferi*. We tested the sera of 68 subjects with rheumatoid arthritis, 147 subjects with other autoimmune diseases, and 44 healthy subjects who had never had Lyme

Molecular mimicry in chronic neuroborreliosis

Hemmer et al. demonstrated that several T-cell clones responded to Borrelia peptides and endogenous host peptides

Table 4 Sequence, potency, and function of human autoantigenic mimics

Sequence	Potency		PB PP[c]	Definition	Notes	Reference or submission
	EC_{50} µg/ml[a]	% of max. response[b]				
(23) YSICKSGCFY	0.1-1	nt	nt	Myelin-associated oligodendrocyte basic protein (MOBP)	Third-most-abundant protein in CNS compact myelin	ref. 45
(61) LHIISKRVEA	0.1-1	70.0	0	titin	Giant protein involved in muscle ultrastructure and elasticity	ref. 46
(62) SFIYSVVCLV	0.1-1	75.7	9	Somatostatin receptor isoform 1	Somatostatinergic neurotransmission modulates cognitive function and may be defective in Alzheimer disease	ref. 47
(63) GHIKKKRVEA	1-10	56.5	0	Transforming growth factor (TGF)-β3	Potent immunosuppressive cytokine; TGF-β3 is mainly expressed in cells of mesenchymal origin	ref. 48
(64) FNITSSTCEL	0.1-1	66.3	1	Human C-C chemokine receptor type 7 precursor	Lymphoid-specific EBV-induced G protein-coupled receptor; upregulated during dendritic cell maturation	refs. 49,50
(66) ENVKKSRRLI	0.1-1	64.1	0	Interleukin (L)-1 receptor type 1, precursor	Receptor for IL-1α and IL-1β; type I membrane protein;binding to agonist leads to activation of NFκB	ref. 51
(71) DNITSSVLFN	0.1-1	60.6	5	Aminopeptidase A	Cleaves acidic amino acids off N terminus of polypeptides (angiotensin II, IL-8, CCK-8); may cleave both IL-7 and IL-7R (N-terminal E); EC 3.4.11.7; genomic structure similar to CD10, CD26; marker of immature B cells, upregulated by IL-7, viral transformation, type I interferons.	refs. 52,53

Source: Hemmer B, Gran B, Zhao Y et al. Identification of candidate T-cell epitopes and molecular mimics in chronic Lyme disease. Nat Med 1999; 5: 1375–1382

Anti-axonal IgM antibodies have been found in the serum of patients with neurological Lyme disease

very uncommon (19, 22). The inability to find the organism in biopsies of affected nerve tissue may indicate that very few organisms are present but that they are nonetheless capable of producing signific
isms has been the
23). Vasculitis in
and may be part
tively, or as a con
is no longer, or wa
and that immune
onopathy; we ha
might be an active
Previous studies have demonstrated that patients with LD-associated neuropathy have serum and cerebrospinal fluid antibodies to *B. burgdorferi* flagellin, often binding to the H9724-defined epitope (7); this epitope cross-reacts with human peripheral nerve axon (36). These antibodies bind to a specific axonal target, a protein with an appro
64 kDa (34), now known to be cpn60
protein (8).

We demonstrated that H9724, a m
shared flagellin-cpn60 epitope, modifies in vitro neurite out-

compatible with the premise that H9724 has its effect at a site proximal to effects mediated by cAMP and protein kinase (activated directly by phorbol esters) or that the effect of
ore physiological pathway. Heat shock
spontaneous neuritogenesis, an obser-
pn60, or a related protein, may play a

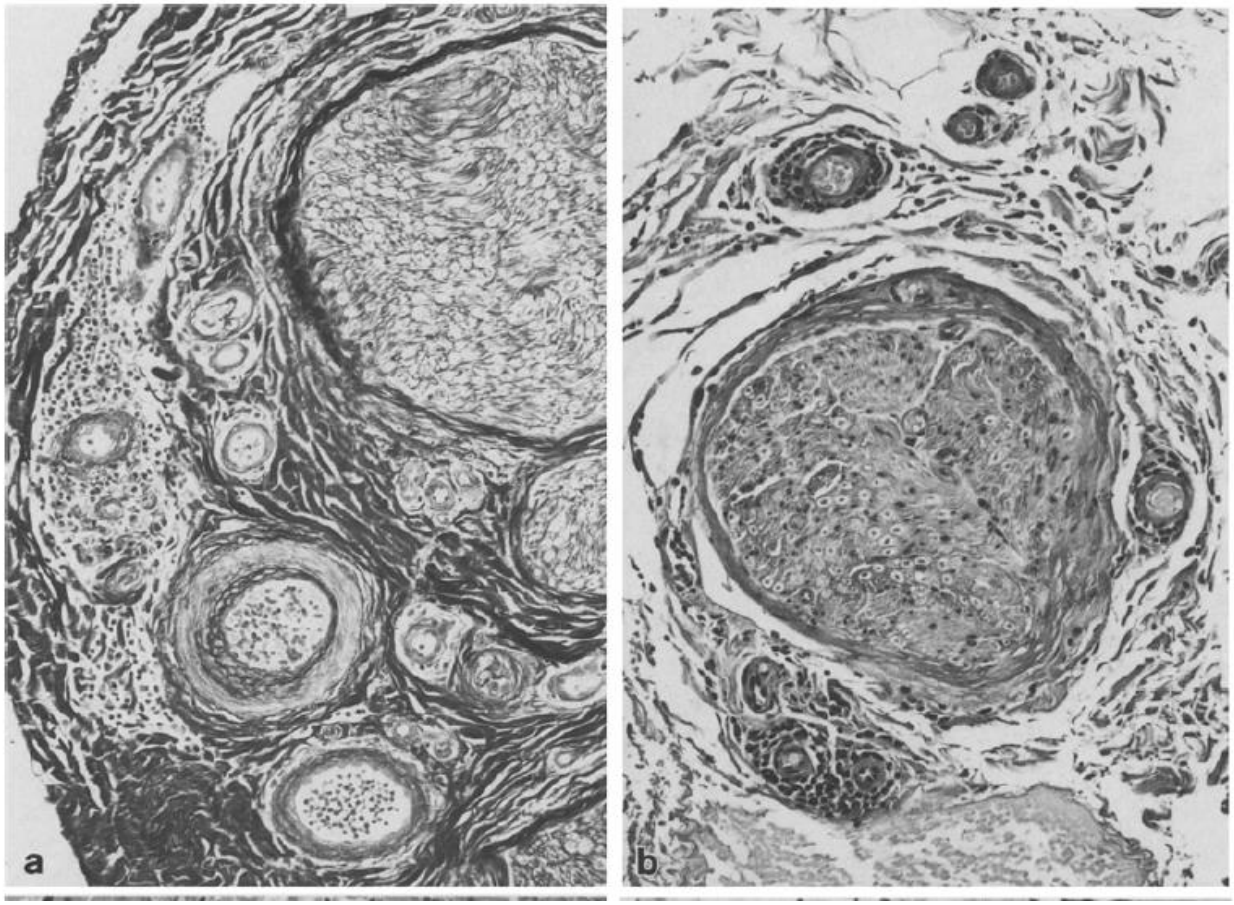
an intracellular protein, although in
r a homolog, can be expressed on the
ed on other studies, including surface
ography, we have concluded that the
nulated SK-N-SH cells is intracellular (data not shown). Certainly, it would be difficult to explain interference with neurite formation on the basis of surface binding of H9724, but that remains a possibility. Our results are compatible with the premise that H9724 is capable of entering the live cultured cells being studied without perma-
ntibody into living neu-
ously (12, 13, 21) and in
ediated by surface Fcγ
ffect on neuritogenesis,
the effects of H9724 are antigen specific and do not represent

"Previous studies have demonstrated that patients with LD-associated neuropathy have serum and **cerebrospinal fluid antibodies** to *B. burgdorferi* flagellin, **often binding to the H9724-defined epitope**"

The H9724-defined epitope cross-reacts with human peripheral nerve axons*

*Source: Sigal LH[1], Williams S A monoclonal antibody to Borrelia burgdorferi flagellin modifies neuroblastoma cell neuritogenesis in vitro: a possible role for autoimmunity in the neuropathy of Lyme disease Infect Immun. 1997 May;65(5):1722-8. ; Dai, Z. Z. (1993). Definition of the Epitope on the 41-kDa Flagellin of Borrelia burgdorferi for a Monoclonal Antibody H9724 and Identification of a H9724-Reactive ProteinFromCalf Adrenal Gland, PhDThesis, Rutgers University 4; * :Sigal, L. H., and A. H. Tatum. 1988. Lyme disease patients' serum contains IgM antibodies to Borrelia burgdorferi that cross-react with neuronal antigens. Neurology 38:1439–1442*

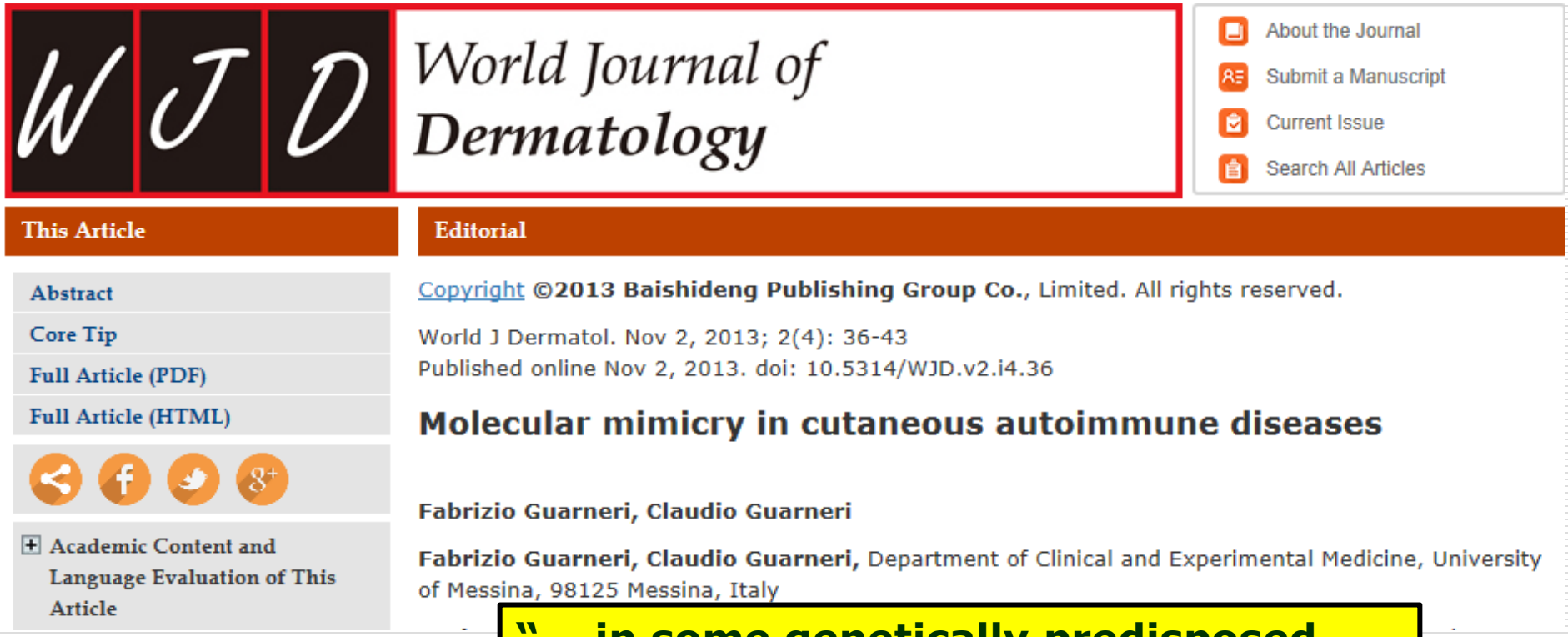
Vasculitis in affected nerves has been reported as part of the neuropathological process



Perivasculitis of epineurial vasa nervorum in sural nerve biopsies from patients with PNS complications of Lyme Borreliosis

Source: Meier, C., F. Grahmann, A. Engelhardt, and M. Dumas. 1989. Peripheral nerve disorders in Lyme-borreliosis: nerve biopsy studies from eight cases. Acta Neuropathol. 79:271–278; Camponovo F, Meier C (1986) Neuropathy of vasculitic origin in a case of Garin-Bujadoux-Bannwarth syndrome with positive borrelia antibody response. J Neurol 233: 69- 72

Borrelia burgdorferi can cross-react with thyroid tissue, triggering Hashimoto's



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Editorial

World J Dermatol. Nov 2, 2013; 2(4): 36-43
Published online Nov 2, 2013. doi: 10.5314/WJD.v2.i4.36

Molecular mimicry in cutaneous autoimmune diseases

Fabrizio Guarneri, Claudio Guarneri

Fabrizio Guarneri, Claudio Guarneri, Department of Clinical and Experimental Medicine, University of Messina, 98125 Messina, Italy

"... in some genetically predisposed subjects, Borrelia infection can be the trigger of Hashimoto's thyroiditis and/or lichen sclerosus"

IgG antibodies that cross-react with myelin basic protein discovered in sera from LD patients

Sera from Lyme disease patients contain antibodies to Bb that crossreact with nervous tissue antigens. Sigal and Tatum found IgM antibodies that cross-reacted with axonal antigens, and Garcia-Monco et al. found IgG antibodies that cross-reacted with myelin basic protein

LYME BORRELIOSIS AND MULTIPLE SCLEROSIS: ANY CONNECTION?
A SEROEPIDEMIC STUDY

Jolanta Chmielewska-Badora, Ewa Cisak, Jacek Dutkiewicz

Department of Occupational Biohazards, Institute of Agricultural Medicine, Lublin, Poland

Chmielewska-Badora J, Cisak E, Dutkiewicz J: Lyme bo
any connection? A seroepidemic study. *Ann Agric Envir*

Abstract: A total of 769 adult neurological patients hosp
situated in the Lublin region (eastern Poland) were exa
2000 with ELISA test for the presence of anti-*Bo*
antibodies. A statistically significant (p = 0.0422) relati
clinically confirmed diagnosis of multiple sclerosis and
with *Borrelia* antigen. Ten out 26 patients with multi
positive serologic reaction to *Borrelia*, whereas among the total number of examined

"A statistically significant (p=0.0422) relationship was found between the clinically confirmed diagnosis of multiple sclerosis and the positive serologic reaction with Borrelia antigen"

Source: Meier, C., F. Grahmann, A. Engelhardt, and M. Dumas. 1989. Peripheral nerve disorders in Lyme-borreliosis: nerve biopsy studies from eight cases. Acta Neuropathol. 79:271–278; Sigal, L. H., and A. H. Tatum. 1988. Lyme disease patients' serum contains IgM antibodies to Borrelia burgdorferi that cross-react with neuronal antigens. Neurology 38:1439–1442; Garcia-Monco JC, Coleman JL, Benach JL (1988) Antibodies to myelin basic protein in Lyme disease. J Infect Dis 158 : 667- 668

Borrelia burgdorferi as well as viruses associated with neurological disease

- Clear role in neurodegenerative and neurobehavioural conditions
- Alzheimer's
- Parkinson's/Parkinsonism
- ALS/motor neurone disease
- ...

Professor Garth Nicolson: clear role of Bb in neurodegenerative and neurobehavioural disease

BJMP.org
British Journal of Medical Practitioners

Role of Chronic Bacterial and Viral Infections in Neurodegenerative, Neurobehavioral, Psychiatric, Autoimmune and Fatiguing Illnesses: Part 1

Garth L. Nicolson and Jörg Haier

Cite this article as: BJMP 2009:2(4) 20-28
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Abstract

Chronically ill patients with neurodegenerative, n
central nervous system bacterial and viral infectio
are routinely found, such as fatiguing and autoim
bacterial and viral infections that could be import
severity of signs and symptoms. Evidence of *Myc*
herpesvirus-1, -6 and -7 and other bacterial and
were not found in controls. Although the specific
have not been carefully determined, the data sug
progressive chronic diseases.

Role of Chronic Bacterial and Viral Infections in Neurodegenerative, Neurobehavioural, Psychiatric, Autoimmune and Fatiguing Illnesses: Part 2

Garth L. Nicolson and Jörg Haier

Cite this article as: BJMP 2010;3
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"Evidence of *Mycoplasma* species, *Chlamydia pneumoniae*, *Borrelia burgdorferi*, human herpesvirus-1, -6 and -7 and other bacterial and viral infections revealed high infection rates in the above illnesses that were not found in controls."

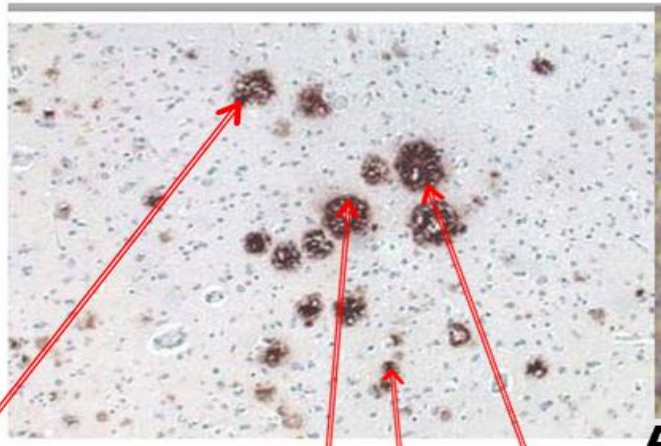
Abstract

Chronically ill patients with ne and
central nervous system bacte ons
are routinely found, such as f nic
bacterial and viral infections t of
signs and symptoms. Evidence of *Mycoplasma* species, *Chlamydia pneumoniae*, *Borrelia burgdorferi*, human herpesvirus-1, -6 and -7 and other bacterial and viral infections revealed high infection rates in the above illnesses that were not found in controls. Although the specific roles of chronic infections in various diseases and their pathogeneses have not been carefully determined, the data suggest that chronic bacterial and/or viral infections are common features of progressive chronic diseases.

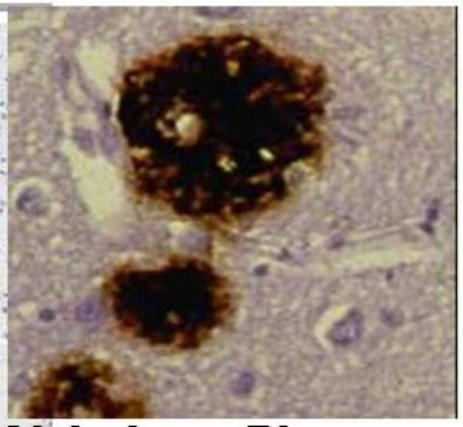
Abbreviations: Ab Beta Amyloid; AD Alzheimer's Disease; ADHD Attention-Deficit Hyperactivity Disorder; ALS Amyotrophic Lateral Sclerosis; ASD Autism Spectrum Disorders; EBV Epstein-Barr Virus; CFS Chronic Fatigue Syndrome; CFS/ME Chronic Fatigue Syndrome/Myalgic Encephalomyopathy; CI Confidence Interval; CMV Cytomegalovirus; CSF Cerebrospinal Fluid; CNS Central Nervous System; ELISA Enzyme Linked Immunoabsorbant Assay; GS Guillain-Barré

Alzheimer Plaques can be Borrelia biofilms

Dr Alois Alzheimer – with Morphing of Alzheimer plaques on his portrait

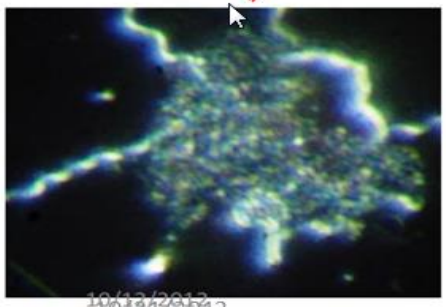


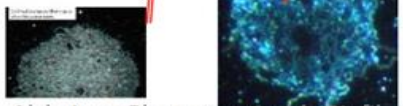
Alzheimer plaques - google



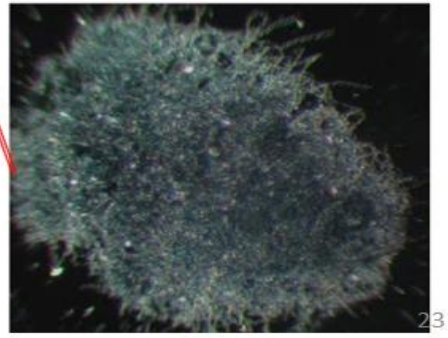
Alzheimer Plaques - Close Up

Borrelia Biofilm Units





Alzheimer Plaques resemble Biofilms of borrelia burgdorferi



Amyloid plaques in Alzheimer's Disease: Protection against microbial infection?

"When you look in the plaques, each one had a single bacterium in it," says Tanzi. "A single bacterium can induce an entire plaque overnight."

"Our findings raise the intriguing possibility that Alzheimer's pathology may arise when the brain perceives itself to be under attack from invading pathogens"

Numerous studies have found connections with Parkinson's/Parkinsonism

Parkinsonism Relat Disord. 2015 Aug;21(8):877-81. doi: 10.1016/j.parkreldis.2015.05.015. Epub 2015 May 30.

The association between infectious burden and Parkinson's disease: A case-control study.

Bu XL[1], Wang X[1], Xiang Y[1], Shen LL[1], Wang QH[1], Liu YH[1], Jiao SS[1], Wang YR[1], Cao HY[1], Yi X[1], Liu CH[1], Deng B[1], Yao XQ[1], Xu ZQ[1], Zhou HD[1], Wang YJ[2].

Author information

Abstract

INTRODUCTION: The etiology of Parkinson's disease is common pathogenic infections and PD.

METHODS: Antibody titers to common infectious pathogens type-1 (HSV-1), Borrelia burgdorferi (B. burgdorferi), measured by ELISA in serum of 131 PD patients and exposure to these common pathogens.

RESULTS: Seropositivities toward zero-two, three-four and five-six of these pathogens were found in 11%, 74% and 15% of normal controls while in 4%, 61% and 35% of PD patients, respectively. IB, bacterial burden and viral burden were independently associated with PD. Schwab and England (S&E) scores were negatively correlated with IB in patients with PD. Serum α-synuclein protein levels and inflammatory cytokines (interleukin-1β and interleukin-6) in individuals with higher IB were also significantly higher.

CONCLUSIONS: IB consisting of CMV, EBV, role of infection in the etiology of PD.

"Infectious burden consisting of CMV, EBV, HSV-1, B. burgdorferi, C. pneumoniae and H. pylori is associated with PD. This study supports the role of infection in the etiology of PD."

Drosophila-like 4 gene, which is associated with inflammation and neuronal death and is up-regulated in Parkinson's disease, was up-regulated in spirochete-stimulated tissues by 9.98-fold*

*Source: * Ramesh G et al. Interaction of the Lyme Disease Spirochete Borrelia burgdorferi with Brain Parenchyma Elicits Inflammatory Mediators from Glial Cells as Well as Glial and Neuronal Apoptosis. Am J Pathol. 2008 Nov; 173(5): 1415–1427*

MND may be associated with Borrelia and coinfections: Patient recovered when treated accordingly

Acta Neurol Scand. 2007 Feb;115(2):129-31.

Motor neuron disease recovery associated with IV ceftriaxone and anti-Babesia therapy.

Harvey WT[1], Martz D.

Author information

Abstract

This report summarizes what we believe to be the first verifiable case of a significant and progressive motor neuron disease (MND) consistent with amyotrophic lateral sclerosis that resolved during treatment with i.v. ceftriaxone plus oral atovaquone and mefloquine. The rationale for use of these antibiotics was (i) positive testing for Borrelia burgdorferi and (ii) red blood cell ring forms consistent with Babesia species infection. The patient has continued to be free of MND signs and symptoms for 15 months, although some symptoms consistent with disseminated Borreliosis remain.

Comment in

Motor neuron disease. [Acta Neurol Scand. 2008]

"… positive testing for Borrelia burgdorferi ….. The patient has continued to be free of MND signs and symptoms for 15 months, although some symptoms consistent with disseminated Borreliosis remain."

Viral involvement in autoimmunity is well documented

- Examples:
  - SLE (Lupus)
  - Ulcerative colitis
  - Sarcoidosis
  - Grave´s disease

EBV and SLE

Arthritis Research & Therapy

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Patients with systemic lupus erythematosus have abnormally elevated Epstein–Barr virus load in blood

Uk Yeol Moon†, Su Jin Park†, Sang Taek Oh, Wan-Uk Kim, Sung-Hwan Park, Sang-Heon Lee, Chul-Soo Cho, Ho-Youn Kim, Won-Keun Lee and Suk Kyeong Lee

† Contributed equally

Arthritis Res Ther 2004 **6**:R295 | **DOI:** 10.1186/ar1181

Received: 4 November 2003 | **Accepted:** 1 April 2004 | **Published:** 7 May 2004

Abstract

Various genetic and environmental factors appear to be involved in systemic lupus erythematosus (SLE). Epstein–Barr virus (EBV) is among the environmental factors that are suspected of predisposing to SLE, based

SLE: Parvovirus B19, CMV, HSV 1/2, VZV

Medicine (Baltimore). 2008 Nov;87(6):311-8. doi: 10.1097/MD.0b013e31818ec711.

Acute viral infections in patients with systemic lupus erythematosus: description of 23 cases and review of the literature.

Ramos-Casals M[1], Cuadrado MJ, Alba P, Sanna G, Brito-Zerón P, Bertolaccini L, Babini A, Moreno A, D'Cruz D, Khamashta MA.

Author information

Abstract

Few studies have evaluated the impact of viral infections on the daily management of patients with systemic lupus erythematosus (SLE). We analyzed the etiology and clinical features of acute viral infections arising in patients with SLE and their influence on the diagnosis, prognosis, and treatment of SLE. Cases occurring within the last 5 years were selected from the databases of 3 large teaching hospitals. Acute viral infections were confirmed by the identification of specific antiviral IgM antibodies and subsequent seroconversion with detection of specific IgG antibodies. In autopsy studies, macroscopic findings sugg sue samples. We performed a MEDLINE search for addit from our clinics and 65 from the literature review) of acute v SLE (fulfillment of the 1997 SLE criteria) associated with int us (EBV; n = 3), and hepatitis A virus (n = 1). The remain patients, symptoms related to infection mimicked a l conditions, presented organ-specific viral infections (m tiorgan process similar to that described in catastrophic antiphospholipid syndrome-the final diagnosis was hemophagocytic syndrome in 5 cases and disseminated viral infection in 5. Twelve patients died due to infection caused by CMV (n = 5), herpes simplex virus (n = 4), EBV (n = 2), and varicella zoster virus (n = 1). Autopsies were performed in 9 patients and disclosed disseminated herpetic infection in 6 patients (caused by herpes simplex in 4 cases, varicella in 1, and CMV in 1) and hemophagocytic syndrome in 3. A higher frequency of renal failure (54% vs. 19%, p = 0.024), antiphospholipid syndrome (33% vs. 6%, p = 0.023), treatment with cyclophosphamide (82% vs. 37%, p = 0.008), and multisystemic involvement at presentation (58% vs. 8%, p < 0.001); and a lower frequency of antiviral therapy (18% vs. 76%, p < 0.001) were found in patients who died, compared with survivors. The most common viral infections in patients with SLE are parvovirus B19 (predominantly mimicking SLE presentation) and CMV (predominantly presenting in severely immunosuppressed patients). CMV infection may mimic a lupus flare or present with specific organ involvement such as gastrointestinal bleeding or pulmonary infiltrates. Other herpesviruses are common in immunosuppressed SLE patients and may produce a wide range of manifestations. Physicians should examine the pharynx, eyes, skin, and genitalia and should conduct serologic and molecular studies to improve early detection of viral infection in patients with SLE.

"The most common viral infections in patients with SLE are parvovirus B19 (predominantly mimicking SLE presentation) and CMV (predominantly presenting in severely immunosuppressed patients)."

EBV / CMV and SLE: Practical example

Untersuchung	Ergebnis	Einheit	Normbereich	Grafik
Autoantikörper				
4 **Antinukl. Antikörper/ANA (IFT~+**	1:3200		< 1:100	[..... *>
4 ANA-Fluoreszenzmuster~	homogen			

Nachweis von antinukleären Autoantikörpern. Der positive ANA-Nachweis kann als e i n Diagnosekriterium für einen Systemischen Lupus Erythematodes herangezogen werden. Dieser Befund kann auch bei anderen Autoimmunerkrankungen (weitere Kollagenosen, chronische aktive Hepatitis, Rheumatoide Arthritis u.ä.) beobachtet werden.
Die Untersuchung auf Autoantikörper gegen dsDNS und ENA ist bei klinischem Kollagenoseverdacht angezeigt! Bei ANA mit homogenem Muster und V.a. Rheumatoide Arthritis ist die Bestimmung des Rheumafaktors und der CCP-Antikörper sinnvoll.

EBV EliSpot (lytisch+latent)

1 **EBV-lytischer Peptidmix**	!	2	SI

0-1 = negativ
2-3 = grenzwertig
ab 4 = positiv

1 **EBV-latenter Peptidmix**	!	9	SI

0-1 = negativ
2-3 = grenzwertig
ab 4 = positiv

Mittels EliSpot finden sich aktuell positive T-Zell-Reaktionen gegen Epstein Barr Virus (EBV).

Erläuterung EBV-Antigene:
EBV lytisches Antigen: Hinweis auf EBV-Replikation
EBV latentes Antigen: Hinweis auf EBV-Latenz

Achtung: Ab 01.08.2016 geänderte Nachweisgrenze!

CMV EliSpot

1 **CMV Peptidmix**	!	21	SI

0-1 = negativ
2-3 = grenzwertig
ab 4 = positiv

Ulcerative colitis: CMV, HSV and EBV

World J Gastroenterol. 2016 Feb 14; 22(6): 2030–2045.
Published online 2016 Feb 14. doi: 10.3748/wjg.v22.i6.2030
PMCID: PMC4726676

Cytomegalovirus and ulcerative colitis: Place of antiviral therapy

Sylvie Pillet, Bruno Pozzetto, and Xavier Roblin

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This article has been cited by other articles in PMC.

Dig Liver Dis. 2001 Oct;33(7):551-8.

Evidence of Epstein-Barr virus infection in ulcerative colitis.

Bertalot G[1], Villanacci V, Gramegna M, Orvieto E, Negrini R, Saleri A, Terraroli C, Ravelli P, Cestari R, Viale G.

Abstract

Go to:

The link between cytomegalovirus (CMV) infection and inflammatory bowel diseases remains an important subject of debate. CMV infection is frequent in ulcerative colitis (UC) and has been shown to be potentially harmful. CMV reactivation needs to be diagnosed using methods that include *in situ* detection of viral markers by immunol
the density of infection using
particularly important. Altho
flare-ups of refractory UC, a
situation. The presence of co
other immunosuppressive ag
to favor CMV reactivation, v
drugs. According to these fir
presence of CMV reactivatic
ganciclovir in cases of high v

Gene Cell Tissue. 2015 October; 2(4): e32846. doi: 10.17795/gct-32846
Published online 2015 October 28. Letter

Investigation of Ulcerative Colitis for Herpes Simplex Virus and Cytomegalovirus Genomic Sequences by the Polymerase Chain Reaction

Sahar Mehrabani-Khasraghi,[1,*] Mitra Ameli,[2] and Farzad Khalil

[1]Department of Microbiology, Tonekabon Branch, Islamic Azad University, Tonekabon, IR Iran
[2]Department of Medicine, Tonekabon Branch, Islamic Azad University, Tonekabon, IR Iran
[3]Gastroenterology and Hepatology Research Center, Alborz University of Medical Sciences, Karaj, IR Iran

*Corresponding author: Sahar Mehrabani-Khasraghi, Department of Microbiology, Tonekabon Branch, Islamic Azad Un
+98-1154274415, E-mail: saharmehrabani1@gmail.com

Received 2015 August 31; **Revised** 2015 September 29; **Accepted** 2015 September 29.

"….the importance of herpes virus, as an exacerbating factor of UC, has been neglected by many clinicians."

Sarcoidosis: EBV, CMV, HSV ...

Box 1 Suspected Causes of Sarcoidosis	
Infectious	**Noninfectious**
Mycobacteria	Dusts
Tuberculous	Clay
Nontuberculous*	Pine
Cell-wall deficient (L-forms)*	Pollen
Bacteria	Talc
Corynebacterium spp.	Mixed*
*Propionibacterium acnes**	Metals
Tropheryma whippleii	Aluminum
Others	Beryllium‡
Fungi	Zirconium
Cryptococcus spp.	
Endemic fungi	
Viruses	
Cytomegalovirus	
Epstein-Barr virus	
Herpes simplex virus	
Others	

*These organisms have been the focus of most recent studies, but no single agent is confirmed. It is very possible that several disparate agents induce similar reactions leading to sarcoidosis.

Source: http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/pulmonary/sarcoidosis/

Graves' Disease and EBV

Viral Immunol. 2011 Apr;24(2):143-9. doi: 10.1089/vim.2010.0072.

The influence of Epstein-Barr virus reactivation in patients with Graves' disease.

Nagata K[1], Fukata S, Kanai K, Satoh Y, Segawa T, Kuwamoto S, Sugihara H, Kato M, Murakami I, Hayashi K, Sairenji T.

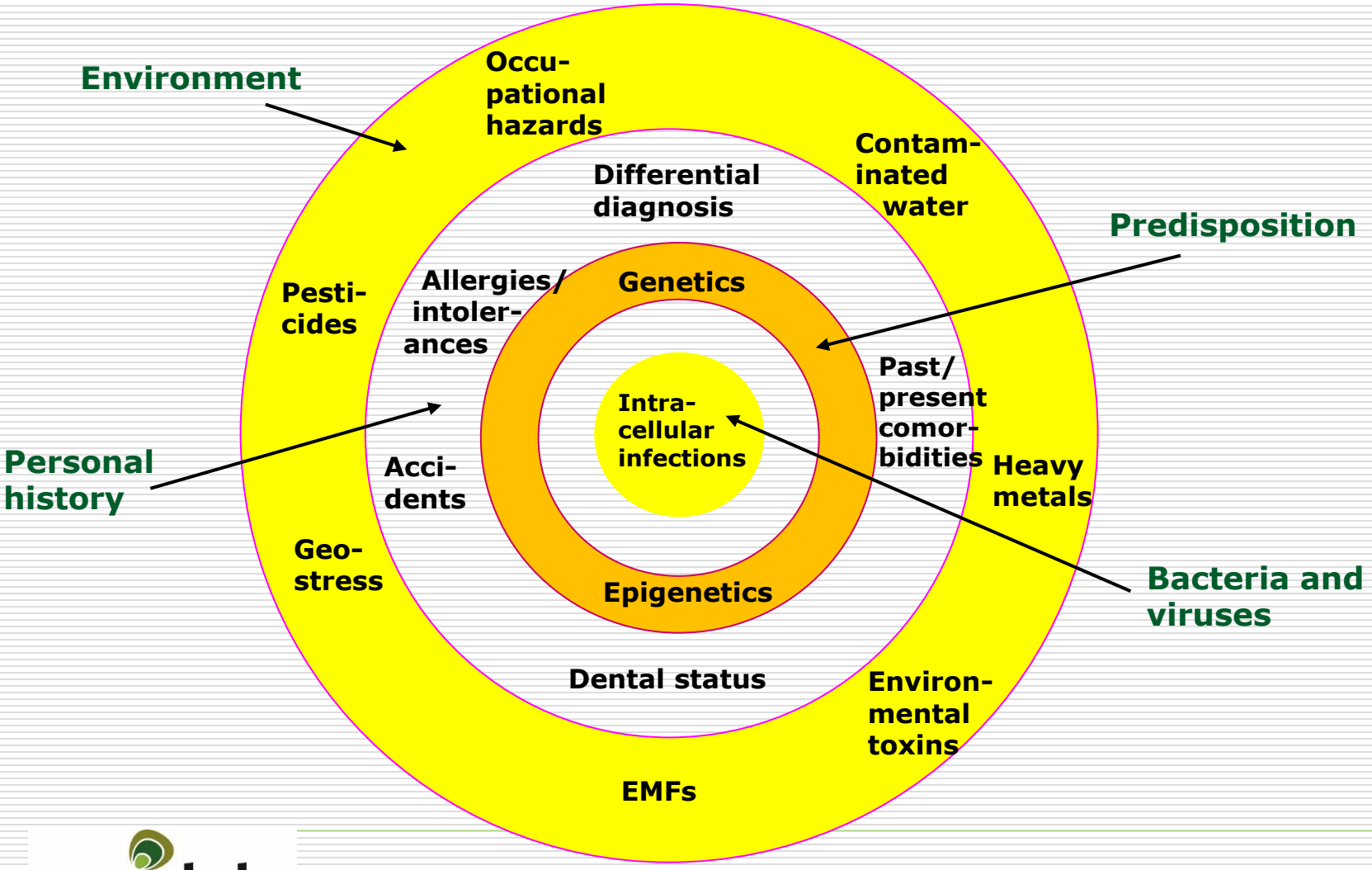
Author information

Abstract

In Graves' disease, the IgG class autoantibody against thyrotropin receptor (TRAb) is produced excessively and induces hyperthyroidism. Epstein-Barr virus (EBV) is one of the human herpesviruses that persists for life, mainly in B lymphocytes, and is occasionally reactivated. Therefore, EBV may affect the antibody production of B lymphocytes that would normally produce TRAb. The purpose of the present study was to evaluate the association of EBV reactivation with the etiology of Graves' disease. Serum levels of EBV antibodies and IgE were determined by ELISA. TRAb levels were determined by radioreceptor assay. We performed in-situ hybridization (ISH) of EBV-encoded small RNA (EBER)1 on the thyroid tissue of one of our patients. In Graves' disease patients with TRAb levels ≥ 10%, EA antibody levels, which indicate EBV reactivation, were moderately but significantly correlated with the levels of TRAb, and weakly but significantly correlated with IgE. EBER1-ISH revealed that one of our patients had EBV-infected lymphocytes infiltrating the thyroid gland. EBV re make TRAb, and this may contribute to or exacerbate the disease.

"In Graves' disease patients with TSH receptor antibodies (TRAb) levels ≥ 10%, EA antibody levels, which indicate EBV reactivation, were moderately but significantly correlated with the levels of TRAb"

„Peeling the onion“



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on 0333 121 0305